REMARKS

I. Claims 1-3, 27-32, 38-41 and 45-47 are pending. In the first rejection, claims 1-3, 27, 28, 30, 31, 38 and 45-47 were rejected. Thus, claims 29, 32 and 39-41 were not rejected in the first rejection. In the second rejection, claims 1, 32, 38-41 and 48-50 were rejected. Claims 48-50 were previously canceled. Thus, claims 2, 3, 27-31 and 45-47 were not rejected in the second rejection.

Claim 29 was not rejected anywhere in the present Office Action. In explaining the two rejections, the Examiner stated that Leboulch et al. mentioned corneal, retinal and iris neovascularization. There was no mention of choroidal neovascularization.

Accordingly, claim 29, which depends on claim 1, and recites that the ocular neovascularization is choroidal neovascularization, was not subject to a rejection and hence, is allowable. The subject matter of claims 1 and 29 was combined in new, allowable claim 51, with cancellation of claim 29. A parallel set of claims similar to those depending on claim 1 was introduced depending on allowable claim 51 as new claims 52-62, which also is allowable.

II. On page 3 of the Office Action, claims 1-3, 27, 28, 30, 31, 38 and 45-47 were rejected under 35 U.S.C. 103(a) over WO99/26480 of Leboulch et al. in view of U.S. Pat. No. 6,555,107.

According to the Examiner, Leboulch et al. teach a method for treating diabetic retinopathy, which can result in corneal, retinal and iris neovascularization, using, for example, a retroviral vector carrying an endostatin sequence which is administered in a manner that allows the vector access to the target cells, such as the retina, page 3, second full paragraph of the Office Action.

In the third full paragraph on page 3 of the Office Action, the Examiner noted that Leboulch et al. do not teach the particular lentivirus, bovine immunodeficiency virus (BIV). The

Examiner thus turned to the '107 patent, which makes passing mention of BIV, to support the rejection. According to the Examiner, the '107 patent teaches that BIV is a preferred vector for transfecting non-dividing cells of the nervous system.

The rejection is traversed for the following reasons.

The use of endostatin according to the claimed invention is not obvious

The instant invention as a whole, inter alia, relates to the use of an endostatin, which at the time of the instant invention, was not viewed as providing a predictable result for reducing the rate of ocular neovascularization because endostatin, in general, had been found not to have an overall biological effect in attempts to beneficially inhibit neovascularization in various types of cancers.[1]

Deere inquiry as to the use of endostatin

According to the paradigm established by the John Deere case, the three steps in an obviousness inquiry are to determine the state of the art, to compare that to the invention; and to determine the level of ordinary skill in the art. (e.g., see MPEP 2141(II), Rev. 6, Sept. 2007)

First step of Deere inquiry into the state of the art on the use of endostatin

It should be noted, as summarized in the Connelly Declaration of 6 February 2006, essentially the only laboratory reporting positive results with endostatin was that of Dr. Judah Folkman, paragraph bridging pages 1 and 2. As noted in the record, a standard for any scientific endeavor, and to establish enablement, is evidence of independent confirmation.

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[1] Applicants agree that Leboulch et al. do not teach or suggest BIV, although Leboulch et al. do mention other, more commonly used, lentiviruses for vector production, such as, HIV and SIV. In the working examples of Leboulch et al., retroviral vectors and not lentiviral vectors were used. The '107 patent makes a solitary reference to BIV in a general discussion of non-primate lentivirus in the background section, see paragraph 6 of the '107 patent.

Most of the evidence in support of the use of endostatin finds origin in the Folkman laboratory, for example, patents naming Dr. Folkman or colleagues, such as, U.S. Pat. Nos. 5,854,205 and 6,174,861; and publications including Dr. Folkman or colleagues as co-authors, such as O'Reilly et al. Thus, generally, the studies of Dr. Folkman were used, at the time of the present invention, to support the studies of Dr. Folkman, including reliance on excerpts of documents, such as from an Introduction or Background[2] of a document from a laboratory not associated with Dr. Folkman, doing no more that referencing studies of the Folkman lab as a rationale for the independent inquiry reported in that document.

Evidence originating from independent laboratories or from former members or colleagues (such as co-authors on publications) of the Folkman lab, such as Drs. Leboulch and Olsen, reporting the inability to duplicate the efforts of Dr. Folkman must be considered probative in determining the state of the art as to endostatin. The totality of the prior art, unrelated to work from the Folkman lab showed that, at the time of the invention, endostatin would not have been expected to significantly inhibit angiogenesis in vivo in a variety of different cancers. In light of that empirical conclusion, the documents, as a whole, cited by the Examiner do not show support for a position that endostatin would have been reasonably expected to ameliorate or to reduce the rate of ocular neovascularization at the time of the invention. To conclude that self-confirmation of the Folkman lab work is evidence endostatin is

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[2] As provided in MPEP 2145, "A conclusion of obviousness requires that the reference(s) relied upon be enabling in that it put the public in possession of the claimed invention," relying on In re Hoeksema, 399 F.2d 269, 274, 158 USPQ 596, 601 (CCPA 1968). Moreover, a reference must be considered as a whole. As with a patent, a publication often prefaces a study with a summary of the art and the reasons for the study. But that is not the focus of the reference, it is the experimentation, the results and the conclusion of a reference which bring value to the public store of knowledge. The references of record, as a whole, teach the heterogeneity of angiogenesis and that endostatin has no meaningful anti-angiogenic activity that would justify developing endostatin as a drug. Hence, for example, Joanneau et al., Eisterer et al. and Bachelot et al., each, as a whole, report the inability to replicate the studies of the Folkman lab. Portions of each publication reference Folkman because the goal of each study was the attempt to replicate the work of the Folkman lab. However, as a whole, each publication reported the inability of independent investigators to find an antiangiogenic effect of endostatin.

enabled, operable and reproducible without taking into account the evidence from others that could not replicate those studies of Dr. Folkman does not provide a true assessment of the state of the art.

Thus, for example, the Connelly Declaration of 6 February 2006 proffered the news article of King et al. published in the Wall Street Journal on 12 November 1998 which summarized the state of the art with regard to the use of endostatin in clinical trials. For example,

> "A number of experts say they haven't been able to verify Dr. Folkman's findings: that an agent called endostatin can cause large tumors in mice to shrink and lie dormant, and this plus a second agent called angiostatin can make such tumors vanish. In science, the critical test of experimental data is that they can be reproduced by other scientists working independently."
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> "One collaborator, the National Cancer Institute, is so concerned about its inability to do so that it had begun to form a panel of outside experts to investigate, when Dr. Folkman agreed to give institute scientists a 10-day demonstration in his lab later this month." (Emphasis ours)
>
> "Meanwhile, Genentech, Inc. scientists tried to duplicate Dr. Folkman's results for a year, then gave up."
>
> "EntreMed Inc., a tiny biotech company that licensed the two biological agents, hired Harvard cell biologist Bjorn Olsen to look into endostatin. Using endostatin variants he made, he couldn't reproduce Dr. Folkman's results, Dr. Olsen[3] says."

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[3] Dr. Olsen was a co-author of Dr. Folkman on, "Endostatin: An Endogenous Inhibitor of Angiogenesis and Tumor Growth" Cell 88:227-285, 1997.

As another example of the inability of an independent laboratory to confirm the results of the Folkman laboratory, Jouanneau et al., J Neuro-Oncol 51:11-18, 2001, of record, published in January of 2001 and cited in the Guo Declaration of 26 March 2007, concluded there is a lack of antitumor activity by endostatin in a human neuroblastoma model. Attempting to replicate the work from the Folkman lab, as noted by the plurality of references from the Folkman lab referenced in the Introduction and Discussion sections of Jouanneau et al., the J Neuro-Oncol paper reported no statistically significant tumor response that correlated with serum endostatin levels. That result was diametrically different from the results of the Folkman lab where regular tumor regression was observed. One of the authors of Jouanneau et al. is Dr. Philippe Leboulch, the same Leboulch who is an author of the primary reference, WO99/26480, grounding the rejection. Therefore, an inventor listed on the primary reference was unable to demonstrate a beneficial effect with endostatin in cancer models. That would clearly lead one skilled in the art to at least conclude there was no reasonable expectation that endostatin could be used to ameliorate or to reduce the rate of ocular neovascularization.

The references above represent a sample of documents attesting to the lack of reproducibility of the work conducted in the Folkman lab that were published prior to the earliest claimed priority date of the instant application. There are other documents, some of which are of record, published after the earliest claimed priority date but relating to studies completed before the priority date, reporting the inability of independent labs to confirm the endostatin research of the Folkman lab. Moreover, studies published subsequent to the filing date of the instant application continue to report the lack of an anti-angiogenic effect of endostatin. Applicants have submitted sworn Declarations which state it was known in the scientific community, that endostatin was commonly ineffective in regressing different tumors in vivo.

Thus, there is substantial evidence of record that the state of the art at the time of the instant invention held endostatin as ineffective in treating different cancers. Hence, it is reasonable to conclude that endostatin was found not to have meaningful anti-angiogenic activity in a number of tissues.

Moreover, Applicants presented in the record, the heterogeneity of angiogenesis from tissue to tissue. For example, Eberhard et al., Canc Res 60:1388-1393, 2000, (cited in the Amendment, filed 9 September 2004, pages 8 and 9) reported on the heterogeneity of angiogenesis among different kinds of cancers. That heterogeneity could have been the result of different mechanisms and thus, different molecules. For example, it was known that fibroblast growth factor, Stegmann, Exp Opin Invest Drugs 7: 2011-2015, 1998; vascular endothelial growth factor (VEGF), Goto et al., Lab Inves 69: 508-17, 1993; matrix metalloproteinase, Am J Physiol Heart Circ Physiol 279: H1540-H1547, 2000; and angiopoietins, Yu & Stamenkovic, Am J Pathol 158:563-570, 2001, and play a role in angiogenesis.

In view of the diverse forms of angiogenesis and the diversity of molecules that have an angiogenic function, and the lack of function of endostatin in one tissue, a conclusion that endostatin would have an anti-angiogenic role in another tissue cannot be supported. Moreoever, the lack of function of endostatin in a number of tissues, albeit cancer tissues, leaves one skilled in the art with no reasonable expectation that endostatin would not have been able to ameliorate or reduce the rate of ocular neovascularization. For example, there is no evidence on the use of endostatin in the eye. There simply is no basis to conclude that at the time of the invention, endostatin would reduce the rate of ocular neovascularization.

Second step of Deere inquiry comparing the state of the art to the invention

Endostatin was tested on a number of tissues, albeit, cancerous forms, and in general, endostatin did not exhibit any substantial anti-angiogenic activity in clinical trials. There is no evidence that an endostatin was successfully shown to ameliorate or to reduce the rate of ocular neovascularization in the eye.

Thus, there are clear differences between the prior art and the claimed invention. Observing a clear reduction of ocular neovascularization by endostatin in the eye, prior to the claimed invention, is not known to have occurred and was not suggested in the cited prior art. In

fact, the prior art, as a whole, casts reasonable doubt that endostatin would have been capable of significantly reducing the rate of neovascularization in a particular tissue.

Third step of Deere inquiry determining the level of skill in the art

As noted in MPEP 2141.03, "Factors that may be considered in determining the level of ordinary skill in the art may include: (A) "type of problems encountered in the art;" (B) "prior art solutions to those problems;" (C) "rapidity with which innovations are made;" (D) "sophistication of the technology"; and (E) "educational level of active workers in the field"."

Due to the numerous failures of endostatin in the prior art; the lack of suggested solutions to those failures; and the lack of guidance in the art as to successful use of an endostatin in vivo, such as in the eye, lead to the conclusion that the state of the art commanded a higher level of what would be ordinary skill in the art.

What would be predictable at the time of the invention, based on the art, was <u>not</u> observing any beneficial effect of endostatin to reduce the rate of ocular neovascularization.

KSR guidance for assessing obviousness

The recent KSR decision provides several rationales for determining whether an invention is obvious, 72 Fed. Reg. 57526, 2007. For example, there is one rationale that could be considered applicable to the instant application.

The claimed invention is not a simple substitution of one known element for another to obtain <u>predictable results.</u>

The MPEP states,

> To reject a claim based on this rationale [simple substitution of one known element for another to obtain predictable results], Office personnel must resolve the Graham factual inquiries. Then, Office personnel must articulate the

> following: . . . a finding that one of ordinary skill in the art could have substituted one known element for another, and the results of the substitution would have been predictable; . . . .
>
> The rationale to support a conclusion that the claim would have been obvious is that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art. (MPEP 2143(B)) (Emphasis ours)

The MPEP further states,

> [t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007) (MPEP 2143.01(III).)

As noted in the first full paragraph on page 4 of the Office Action, the Examiner stated it would have been prima facie obvious to substitute the BIV vector taught in the '107 patent for the vectors taught in Leboulch et al. to obtain the claimed invention.

First, it can be seen that the teachings of the two references do not justify the rejection. For example, as summarized above, the state of the art as to endostatin was that there was no reasonable expectation that endostatin would be able to reduce the rate of neovascularization in any one tissue, and certainly not in a tissue such as the eye. Thus, reliance on Leboulch et al. as provided in the rejection does not take into account the state of the art as to endostatin at the time of the invention. That lack of success with endostatin would rule out use of Leboulch et al. as a reference against the instant application because the wealth of studies, at the time of the invention and even shortly thereafter, determined endostatin not to have a substantial antiangiogenic activity in a variety of tissues. The '107 patent does not cure that deficiency.[4]

[4] The reliance on the '107 patent for teaching a BIV vector is incorrect. The focus of the '107 patent as a whole is FIV vectors. The only mention of BIV is in the Background of the '107 patent where

Therefore, there is no basis to conclude an artisan could substitute one known element for another with predictable results.

Accordingly, under that rationale, a prima facie case of obviousness has not been made.

Secondary considerations

Even if, arguendo, a prima facie case of obviousness were made, there are several secondary considerations that speak to non-obviousness of the claimed invention, such as, satisfaction of a long felt and unsolved need; the prior failed attempts of others; and the unexpectedness of the claimed invention. Those secondary considerations rebut and overcome any such hypothetical prima facie case of obviousness.

Satisfaction of a long felt and unsolved need

The treatment of cancer, and more recently ocular neovascularization are long standing, persistent and continuing goals of medicine. Aberrant neovascularization or neovascularization per se has been associated with pathology. Hence, controlling neovascularization or aberrant neovascularization, the cause or a symptom of a pathology has been a long standing goal and avenue for drug development.

The instant invention resurrects endostatin and provides a reduced rate of ocular neovascularization. The success demonstrates that endostatin, under certain circumstances does have a beneficial impact on aberrant neovascularization as found, for example, in macular degeneration in the eye.

BIV was included in a list of non-primate lentiviruses. Beyond that one instance, there is no teaching or guidance in the '107 patent for making and using a BIV vector.

Thus, the '107 does not teach a BIV vector and provides no reasonable basis to conclude that one of skill could have predictably made a BIV vector based on the teachings of the '107 patent.

Prior failed attempts of others

The long felt and unsatisfied need dovetails with another secondary consideration, the prior failed attempts of others. As noted hereinabove, for example, Jouanneau et al., the Wall Street Journal article, and other references of record, show that many have attempted to duplicate the studies of the Folkman lab without success. Since the believed mechanism of action for endostatin in cancer treatment was inhibiting/reducing the rate of neovascularization, one in the art at the time of the invention, would not have had a reasonable expectation that endostatin could ameliorate or reduce the rate of ocular neovascularization.

Unexpectedness of the claimed invention

As provided in the Kaleko Declaration of 7 February 2006, the endostatin construct was used merely to validate the BIV vector as able to successfully infect cells of the eye. The only expectation was for endostatin to be expressed and detected with an endostatin antibody. No one expected there to be an anti-angiogenic activity of endostatin based on the prior art, and thus even the co-inventors were surprised that a biological effect was observed on expression of the endostatin in the eye.

Teaching away

The numerous independent publications reporting an inability to duplicate the results of the Folkman lab and the failure of their Phase II clinical trials to show efficacy of endostatin in treating any of a variety of cancers (for example, see Kulke et al., J Clin Oncol 24:3555-3561, 2006, reporting no antiangiogenic effect using recombinant endostatin in patients with advanced neuroendocrine tumors, none of 40 patients assessable for radiologic response experienced even a partial response to therapy) teach away from using endostatin as a drug candidate for the reducing ocular neovascularization.

Secondary considerations overcome any prima facie case of obviousness

Hence, the secondary considerations clearly speak to the unexpectedness and hence, to the non-obviousness of the claimed invention. Those secondary considerations overcome any hypothetical prima facie case of obviousness.

Accordingly, withdrawal of the rejection is in order.

III. On page 4 of the Office Action, claims 1, 32, 38-41 and 48-50 were rejected under 35 U.S.C. 103(a) over WO99/26480 of Leboulch et al. in view of U.S. Pat. No. 6,555,107 and further in view of U.S. Pat. No. 6,106,826.

According to the Examiner, Leboulch et al. teach a method for treating diabetic retinopathy, which can result in corneal, retinal and iris neovascularization, using a retroviral vector carrying an endostatin sequence, page 4, lines 13-19 of the Office Action. In the first full paragraph on page 5 of the Office Action, the Examiner indicated that Leboulch et al. do not specifically teach the bovine lentivirus, which can be administered intraocularly, subretinally or intravitreally. The Examiner then turned to the '107 patent for an asserted teaching of BIV vectors and then the '826 patent for the modes of administration to the eye.

The rejection is traversed for the following reasons.

The arguments and discussion hereinabove, are herein incorporated by reference in entirety as to the primary and secondary references.

As clearly provided hereinabove, Leboulch et al. and the '107 patent both are deficient as to teaching or suggesting the claimed subject matter. The Leboulch et al. document does not teach or suggest a predictable use of endostatin to one skilled in the art at the time of the invention. The '107 patent does not teach or suggest whether BIV can be used to make a vector,

and how to achieve that goal. Thus, alone or together, Leboulch et al. and the '107 patent are insufficient to ground an obviousness rejection.

The '826 patent is relied on to teach particular modes of drug administration. The '826 patent does not relate to endostatin or to lentivirus. Hence, the '826 patent does not cure the fatal deficiencies of Leboulch et al. and of the '107 patent, taken alone or together.

Clearly a prima facie case of obviousness has not been made. Even if, arguendo, a prima facie case were made, the secondary considerations associated with the claimed subject matter summarized above and herein incorporated by reference in entirety overcome any such hypothetical case of obviousness.

Accordingly, withdrawal of the rejection is requested respectfully.

IV. Reply to "Response to Arguments" of Examiner

At pages 6-8 of the Office Action, the Examiner responded to the previous evidence and arguments of Applicants. Inter alia, the previous remarks of Applicants related to: (i) no reasonable expectation and teaching away (Amendment filed 31 October 2007, pages 5-7); and (ii) that WO99/24680 (Leboulch et al.) is not enabled. Applicants presented, in part, evidence of the failure of those skilled in the art at the time of the invention to replicate the results of the Folkman lab and the teachings of WO99/24680.

In response, the Examiner cited only documents related to the Folkman lab[5]. The Examiner did not address the strong doubt in the art related to the results of the Folkman lab and the teachings of WO99/24680.

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[5] U.S. Patent Nos. 5,854,205 and 6,174,861 have Folkman listed as a co-inventor. O'Reilly et al. has Folkman as a co-author. Jounneau et al. and Bachelot et al., discounting the results of the Folkman lab, both have Leboulch of WO99/24680 as a co-author. Sauter et al. was communicated by Dr. Folkman for publication in the Proceedings of the National Academy of Sciences.

V. Amendments to the claims

As noted above, the only amendment to the claims is the cancellation of non-rejected claim 29, which depended on claim 1; and the addition of new claim 51 which combines the subject matter of claims 1 and 29, along with claims dependent on claim 51. Hence, early indication of allowance of claims 51-62 is requested respectfully.

Because claim 29 is not rejected anywhere in the present Office Action, new claim 51, which relates to the subject matter of non-rejected claim 29, and the claims dependent on claim 51, should the subject matter of claims 51-62 not be considered allowable, cannot be the basis for making any succeeding Office Action final based on a rejection of those new claims. Any rejection of claim 51 is a new rejection not necessitated by the above amendment, since claim 29 is not rejected in the present Office Action. Therefore, Applicants believe a rejection of claims 51-62 must appear in a Non-Final Office Action.

CONCLUSION

Applicants submit that the pending claims are in condition for allowance and early indication of such is requested respectfully. Reexamination, reconsideration, withdrawal of the rejections and early indication of allowance are solicited earnestly.

Respectfully submitted,

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